REMARKS

Claims 1-6, 9, 10 and 17-23 are pending. Claims 7, 8, and 11-16 were previously canceled. Amendment of claims herein is made without abandonment of the original subject matter; Applicants reserve the right to pursue claims of the original or similar scope in a duly filed continuing application. Applicants respectfully request entry of the present amendment.

Claim 1 has been amended to recite the terms "DNA" in place of "nucleic acid" and an "immune response" in place of "response". Support for the amendments to claim 1 is found throughout the specification and at least at page 2, lines 9-11; page 3, lines 23-26; page 4, lines 8-18; page 9, lines 11-19; page 11, line 28; and page 12, lines 16-18 of the application as originally filed.

Claim 3 has been amended to recite the phrase "[t]he *S. typhimurium* strain of claim 2" in place of "[t]he *Salmonella* strain of claim 2." Support for the amendment to claim 3 is found throughout the specification and in claim 2, from which claim 3 depends.

Claim 5 has been amended to recite the phrase "[t]he *S. typhi* strain of claim 4" in place of "[t]he *Salmonella* strain of claim 4." Support for the amendment to claim 5 is found throughout the specification and in claim 4, from which claim 5 depends.

Claim 6 has been amended to remove the phrase "is derived from plasmid pCMVβ, wherein the plasmid. . . ." The amendment is made merely to remove the assertedly confusing use of the term "derived" in the claim.

Claim 9 has been amended to merely remove the hyphens from the terms "*Escherichia coli* ß-galactosidase", "*Listeria monocytogenes* listeriolysin," and *Listeria monocytogenes* actA polypeptide." Claim 23 has been amended merely to remove the hyphen from the term "*Listeria monocytogenes* listeriolysin polypeptide."

Claim 19 has been amended to recite the phrase "wherein the vertebrate is a human" merely to correct the improper antecedent basis for the use of the term "vertebrates" in plural form.

Claim 20 has been amended to recite the phrase "wherein the *Salmonella* strain of claim 1" in place of "wherein *Salmonella* of claim 1." Support for the amendment to claim

20 to depend properly from claim 1 is found throughout the specification and in claim 1, from which claim 20 depends.

Thus, the claim amendments herein find basis in the original specification and claims and no new matter has been introduced.

OUTSTANDING REJECTIONS

Claim 1 was rejected under 35 U.S.C. §112, first paragraph, as assertedly containing new subject matter.

Claims 1-6, 9, 10, and 17-23 were rejected under 35 U.S.C. §112, second paragraph, as assertedly being indefinite.

Claims 1, 2, 4, 6, 9, 10, and 17-22 were rejected under 35 U.S.C. §102(e)(2) as assertedly being anticipated by Powell et al. (U.S. Patent No. 5,877,159, filed May 3, 1995; hereinafter, "Powell").

Claim 3 was rejected under 35 U.S.C. §103(a) as assertedly being anticipated by Powell in view of Fouts et al. (*Vaccine* 13:1697-1705, 1995; hereinafter, "Fouts").

Claim 5 was rejected under 35 U.S.C. §103(a) as assertedly being anticipated by Powell in view of Dyall-Smith et al. (U.S. Patent No. 5,332,658, filed June 16, 1992; hereinafter, "Dyall-Smith").

PATENTABILITY ARGUMENTS

1. The rejections under 35 U.S.C. § 112, first paragraph, for new subject matter

While Applicants disagree with the Examiner for the reasons provided in the prior response, Applicants have amended claim 1 to replace the phrase "a nucleic acid encoding a polypeptide, wherein said nucleic acid" with "DNA, wherein said DNA" solely in order to expedite prosecution. The rejection of claim 1 at pages 4 of the Action is rendered moot by the amendment to claim 1 herein.

2. The rejections under 35 U.S.C. §112, second paragraph

Applicants have amended claim 1, which was rejected for being assertedly confusing in the use of the term "a response." The rejection of claim 1 at page 5 of the Action is rendered moot by the amendment to claim 1 herein to recite "an immune response."

Applicants have amended claim 3, which was rejected for the use of the phrase "the *Salmonella* strain of claim 2, because claim 2 recites "a *S. typhimurium* strain." The rejection of claim 3 at page 5 of the Action is rendered moot by the amendment to claim 3 herein to recite " the *S. typhimurium* strain of claim 2. . .."

Applicants have amended claim 5, which was rejected for the use of the phrase "the *Salmonella* strain of claim 4, because claim 4 recites "a *S. typhi* strain." The rejection of claim 5 at page 5 of the Action is rendered moot by the amendment to claim 5 herein to recite " the *S. typhi* strain of claim 4. . .."

Applicants have amended claim 6, which was rejected for the use of the term "derived". The rejection of claim 6 at page 5 of the Action is rendered moot by the amendment to claim 6 herein to remove the assertedly confusing use of the term in the claim.

Applicants have amended claims 9 and 23, which were rejected for the use of hyphens between the named bacteria and the recited polypeptides. The rejection of claims 9 and 23 at page 5 of the Action is rendered moot by the amendments to claims 9 and 23 herein to remove the hyphens from the claims.

Applicants have amended claim 19, which was rejected for an assertedly improper antecedent basis for the use of the term "vertebrates" in plural form. The rejection of claim 19 at page 5 of the Action is rendered moot by the amendment to claim 19 herein to recite the singular form of "vertebrate" in the claim.

Applicants have amended claim 23, which was rejected for the use of the phrase "a gene (hly gene) encoding a non-hemolytic truncated Listeria moncytogenes-literiolysin gene (hly gene)" to recite the corresponding polypeptide, consistent with the terminology used in amended claim 1. The rejection of claim 23 at page 7 of the Action is believed to be rendered moot by the amendment to claim 23 herein.

The rejection of claims 2-6, 9, 10, and 17-23, which depend directly or indirectly from claim 1, at page 5 of the Action is rendered moot by the amendments to claims 1, 3, 5, 6, 9, 19, and 23 herein.

3. The rejection under 35 U.S.C. §102

Claims 1, 2, 4, 6, 9, 10, and 17-22 were rejected under 35 U.S.C. §102(e)(2) as assertedly being anticipated by Powell at pages 5-7 of the Action. In response, Applicants respectfully disagree.

Despite the Examiner's characterization of the disclosure of Powell, Applicants submit that Powell's disclosure does not enable the presently claimed subject matter and, thus, cannot anticipate the claimed subject matter. When the Patent Office cites prior art as being anticipatory, an applicant can overcome the rejection "by proving that the relevant disclosures of the prior art . . . are not enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). The enablement requirement of 35 U.S.C. § 112, first paragraph, ensures that an application teaches how to make and use the invention as claimed without requiring undue experimentation. The inquiry may be guided by consideration of several factors enumerated in a biotechnology context. *In re Wands* 858 F.2d 731 (Fed. Cir. 1988). In *Wands*, the Federal Circuit set forth a number of factors which a court may consider in determining whether a disclosure would require "undue" experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands* 858 F.2d 731, 737. However, all of the *Wands* factors need not be reviewed when determining whether a disclosure is enabling. *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts."). Applicants submit that applying the "*Wands*" analysis to Powell can only lead to the conclusion that the cited reference does not enable one of ordinary skill in the art to practice the presently claimed invention without undue experimentation.

The nature of the invention, as discussed throughout the specification and as recited in the claims, is an attenuated *Salmonella* strain containing a *eukaryotic expression vector* that comprises a eukaryotic promoter and a DNA, under the control of the eukaryotic promoter, encoding a polypeptide, wherein the administration of the attenuated *Salmonella* strain to a vertebrate results in expression of the polypeptide by the vertebrate and generates an immune response by the vertebrate to the encoded polypeptide.

In arts such as biotechnology, enablement requires more extensive disclosure because of the unpredictability involved in practicing inventions in these arts. *See* generally *Chisum on Patents*, § 7.03[4][d][i], at 7-58 (1999) ("A recurring problem is whether a specification that sets forth a single or a limited number of examples can be enabling of broad claims when the subject matter concerns biological materials or reactions, which are generally considered to be unpredictable.") and cases cited therein; *Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821 (Bd. Pat. App. Interf. 1988) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more is required . . . ."); *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The amount of guidance presented and the presence or absence of working examples are two additional factors relevant to enablement. Powell does not provide any guidance regarding the use of an attenuated *Salmonella* strain containing a *eukaryotic expression vector* that is *effective for generating an immune response.* Instead, Powell apparently provides guidance for the use of an attenuated *Shigella* strain containing a *eukaryotic expression vector* that is *effective for generating an immune response.* Furthermore, Powell does not provide any working examples, either actual or prophetic, which demonstrate that an attenuated *Salmonella* strain containing a *eukaryotic expression vector* can be successfully used to express a heterologous gene in a cell or animal host, much less demonstrate that an attenuated *Salmonella* strain containing a *eukaryotic expression vector* can be successfully used in *generating an immune response.*

Powell states that the bacteria of the invention must have invasive properties, such as those of *Shigella*, and discloses that other bacteria, such as *Salmonella*, must be engineered to be invasive prior to use in the invention (see Powell at column 10, lines 35-46). Powell, however, does not disclose how a *Salmonella* strain should or could be engineered to achieve this result. To the extent that Powell discloses that any bacteria may be used in the invention, the disclosure provides the worker of ordinary skill with little more than an invitation to experiment. Thus, the broad statement, that the particular *Salmonella* strain employed is not critical to the invention, does not provide any guidance as how to practice the invention with any *Salmonella* strain, much less an attenuated strain. "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)).

"Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Id* at 1366.

Moreover, the state of the prior art at the time of the filing of the instant application, as supported by the Declaration of Dr. Siegfried Weiss, under 37 C.F.R. § 1.132 (hereinafter "Declaration"; submitted herewith as **Exhibit A**), actually discouraged the use of *Salmonella* as claimed in the present invention. Like Powell, Branstrom (U.S. Patent No. 5,824,538, filed September 6, 1995; cited by the Examiner in previous Office Actions) disclosed an attenuated *Shigella* strain comprising an expression vector for delivering a mammalian expression plasmid into cells for the generation of an immune response. Notably, Branstrom stated that:

> "Although we have no formal proof that release from the phagocytic vacuole into the cell cytoplasm by the bacteria is essential for DNA delivery, preliminary experiments with ***Salmonella typhurium***, an organism that reaches the cytoplasm only with difficulty, suggest that **this organism is not an efficient DNA delivery vehicle**" (emphasis added).

See Branstrom at column 19, line 40, through column 20, line 4. Thus, prior to the filing of the instant application, a person of ordinary skill in the art, with knowledge of the disclosure in Branstrom, would have been discouraged from using an attenuated *Salmonella* for delivering DNA under the control of a eukaryotic expression vector into cells for immunization of vertebrates whereby the host expresses the antigen. Moreover, Branstrom's statement (recited above), suggesting that *Salmonella* is inefficient for DNA delivery, is repeated by Sizemore et al. in their parallel scientific publication [see *Science* 270:299-302, 1995 at page 301, right column, second paragraph (enclosed as **Exhibit B**)].

In addition, the predictability (or unpredictability) in the art is another factor to consider in deciding whether a disclosure would require undue experimentation. The publication by Lowrie (*Nature Medicine* 4:147-148, 1998; hereinafter "Lowrie"; enclosed with the Response to an Office Action mailed March 11, 2005), previously submitted by Applicants, provides objective evidence that others in the art viewed the claimed invention as unexpected and surprising, and, therefore, unpredictable. Lowrie refers to the publication of Darji et al. [*Cell* 91:765-775 (1997); hereinafter "Darji"], which was authored by the inventors of the present application and discloses the same data as the present application. (Darji was enclosed

with the Response to an Office Action mailed December 10, 2004.) *See* Lowrie at page 147, central column, second paragraph, wherein Lowrie states in referring to the work by Darji that:

> "the **unexpected and marked success of the salmonella DNA delivery vehicle** further challenges the perception that DNA vaccination is abnormal biology and is therefore inherently dangerous. **The success of salmonella is surprising** because – in contrast to shigella and invasive *E. coli*, both of which escape from the phagocytic vacuole to enter the cytoplasm in cells – this bacterium is believed to be retained within the phagolysosome, the normal fate of particles engulfed by phagocytes" (emphasis added).

This publication by Lowrie demonstrates that one of skill in the art found the invention of the instant application, as described in Darji's publication, to not have been predicted or anticipated in light of the prior art.

Based on the above analysis of the *Wands* factors, Powell has not provided an enabling disclosure that would anticipate the claimed subject matter of the instant invention without undue experimentation. The combination of Powell's lack of guidance regarding the use of an attenuated Salmonella strain; Powell's lack of working examples using *Salmonella*; the state of the prior art, which discouraged use of attenuated *Salmonella* for the delivery of genes (DNA) into mammalian cells and vertebrates for the generation of an immune response; and the unpredictability and surprising success of *Salmonella* for the delivery of DNA into cells for the generation of an immune response all lead one to conclude that Powell does not anticipate the claimed subject matter. Consequently, for all the reasons set out above, the rejection of claims 1, 2, 4, 6, 9, 10, and 17-22 under 35 U.S.C. §102(e)(2) for asserted anticipation by Powell should be withdrawn.

4. The rejections under 35 U.S.C. §103

a. The rejection of claim 3 under 35 U.S.C. §103(a)

Claim 3 was rejected under 35 U.S.C. §103(a) as assertedly being unpatentable over Powell in view of Fouts at pages 7-8 of the Action. In response, Applicants respectfully disagree.

According to MPEP §2143, in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Fouts does not remedy the deficiencies in Powell as noted above in section 3, and the Examiner has not contended otherwise. Fouts assertedly discloses an attenuated *S. typhimurium* aroA SL 7207 vaccine strain specifically for expressing a heterologous antigen to elicit a heterologous antigen-specific immune response. However, Fouts does not disclose an attenuated *Salmonella* strain containing a *eukaryotic expression vector* that is *effective for generating an immune response*. Fouts merely discloses an attenuated *S. typhimurium* aroA SL 7207 vaccine strain bearing a heterologous gene under the control of a prokaryotic promoter. The ability of an immunized eukaryotic host to express the gene is an important point of the instant application because that is the mechanism by which the genetic immunization occurs. Applicants' experimental data at pages 8-10 showed that the immune response generated by the vaccine was due to the *in vivo* transfer of the gene and expression of the gene by the mice, not due to the expression of the gene by *Salmonella*.

Thus, Fouts does not disclose an attenuated *Salmonella* strain comprising a eukaryotic expression vector (under control of a eukaryotic promoter), and the combination of Fouts with Powell, for the reasons set out above in section 3, does not teach or suggest all the claim limitations. Moreover, there was no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the teachings of Powell with Fouts to derive the claimed subject matter, and even if combined there was no reasonable expectation of success. For all these reasons, Powell in view of Fouts does not render obvious claim 3 and the rejection should be withdrawn.

b. The rejection of claim 5 under 35 U.S.C. §103(a)

Claim 5 was rejected under 35 U.S.C. §103(a) as assertedly being unpatentable over Powell in view of Dyall-Smith at page 8 of the Action. In response, Applicants respectfully disagree.

As set out in section 4(a) above, MPEP §2143, sets out three basic criteria which must be met in order to establish a *prima facie* case of obviousness: 1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; 2) there must be

some suggestion or motivation to modify the reference or to combine reference teachings; and 3) there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* MPEP §2143.

Like Fouts, as noted above, Dyall-Smith does not remedy the deficiencies in Powell as noted above in section 3. Dyall-Smith assertedly discloses an attenuated *S. typhi* Ty21a vaccine or vector strain specifically for expressing a heterologous gene to elicit a heterologous protein-specific immune response. However, Dyall-Smith does not disclose an attenuated *Salmonella* strain containing a *eukaryotic expression vector* that is *effective for generating an immune response*. Dyall-Smith merely discloses a *S. typhi* Ty21a strain bearing a heterologous gene, VP7, under the control of a prokaryotic promoter. As stated above in Section 4a, the ability of an immunized eukaryotic host to express the gene is an important point of the instant application because that is the mechanism by which the immunization occurs. Applicants' experimental data at pages 8-10 showed that the immune response generated by the vaccine was due to the *in vivo* transfer of the gene and expression of the gene by the mice, not due to the expression of the gene by *Salmonella*.

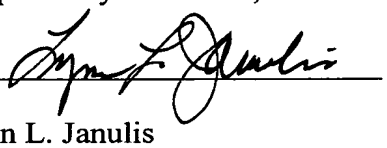
Thus, Dyall-Smith does not disclose an attenuated *Salmonella* strain comprising a eukaryotic expression vector (under control of a eukaryotic promoter), and the combination of Dyall-Smith with Powell, for the reasons set out above in section 3, does not teach or suggest all the claim limitations. Moreover, there was no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine reference teachings to derive the claimed subject matter, and even if combined there was no reasonable expectation of success. For all these reasons, Powell in view of Dyall-Smith does not render obvious claim 5 and the rejection should be withdrawn.

CONCLUSION

For the reasons set out above, each of claims 1-6, 9, 10 and 17-23 is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

Dated: March 28, 2005

Respectfully submitted,

By 

Lynn L. Janulis
Registration No.: 53,066
Agent for Applicants

MARSHALL, GERSTEIN & BORUN, LLP
6300 Sears Tower
233 S. Wacker Drive
Chicago, Illinois 60606
Telephone: (312) 474-6300